PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4-32375A	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP 03/02028	International filing date *(day/month/year)* 27.02.2003	Priority date *(day/month/year)* 28.02.2002
International Patent Classification (IPC) or both national classification and IPC A61L31/16		
Applicant NOVARTIS AG et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.08.2003	21.06.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Muñoz, M Telephone No. +31 70 340-4542

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/02028

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-30 as originally filed

Claims, Numbers

1-15 received on 07.04.2004 with letter of 30.03.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 14,15

   because:

   ☒ the said international application, or the said claims Nos. 14,15 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-13
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-13
Industrial applicability (IA)	Yes:	Claims	1-13
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 14 and 15 are considered by this authority to relate to a method of treatment of the human (or animal) body by therapy as defined in Rule 67(1)(iv) PCT. This International Preliminary Examining Authority, using its discretion, has decided not to formulate an opinion with regard to novelty, inventive step and industrial applicability on the subject-matter of these claims following Article 34(4)(a)(iv) PCT when taken in combination with Article 33(1) PCT.

Re Item V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Claim 10 comprises all the features of claim 9 and should therefore be dependant from it.

2. Reference is made to the following documents:

D1: Myllarniemi Marjukka et al.: "Selective tyrosine kinase inhibitor for the platelet-derived growth factor receptor in vitro inhibits smooth muscle cell proliferation after reinjury of arterial intima in vivo.", *Cardiovascular Drugs and Therapy*, vol. 13(2), **April 1999**, pages 159-168.

D2: WO-A-99/03854 (1999-01-28)

3. D1 relates to selective tyrosine kinase inhibitors and their effect on the inhibition of smooth muscle cell proliferation. CGP57148B, also known as Imatinib mesylate, is specifically disclosed (see page 164, left column-page 165, right column first paragraph). This study is made in the context of avoiding restenosis (see page 159, left column-page 160, left column, first paragraph).

4. D2 discloses the properties of Imatinib mesylate to treat restenosis and for the prevention of transplantation induced disorders such as obliterative bronchiolitis (see pages 9, third paragraph). Galenic formulations of Imatinib mesylate (see examples 3 and 4) are also disclosed.

5. Neither D1 nor D2 disclose the use of Imatinib mesylate for the prevention or

reduction of vascular access disfunction for stabilizing vulnerable plaques in blood vessels.

Neither D1 nor D2 disclose the provision of a drug delivery device with Imatinib mesylate affixed to it.

Thus the subject-matter of claims 1-13 is novel in view of the prior art (Article 33(1) and (2) EPC).

6. The difference between the subject-matter of claim 1 and the teaching of D1, which can be considered as the most relevant prior art, dwells on the provision of **two** further medical uses of Imatinib mesylate, that is the use for stabilizing vulnerable plaques in blood vessels and the prevention or reduction of vascular access dysfunction.

Those further uses, considering the fact that it is known to the skilled person to use Imatinib mesylate in the prevention of transplantation induced disorders and in reducing restenosis cannot be considered as inventive as they rely on a known activity of Imatinib mesylate and the skilled person would have considered those further uses as obvious alternatives.

Thus, the subject-matter of claim 1 is not considered to meet the requirements of inventive activity (Article 33(1) and (3) PCT).

7. The difference between the subject-matter of claims 9 and 10 and the teaching of D1, which can be considered as the most relevant prior art, dwells on the provision of Imatinib in combination with a drug delivery device.

The problem to be solved may therefore be considered as the provision of local delivery means of Imatinib.

The solution proposed by the applicant is the provision of a local delivery device to which Imatinib is releasably affixed.

Local delivery via medical devices is a well known alternative to the skilled person. The skilled person knowing from D1 the anti-restenotic properties of Imatinib would have combined Imatinib with a medical device to achieve local delivery of the drug.

A technical effect is mentionned in Example 5 and relates to the stability of Imatinib mesylate. This technical effect is only mentioned in combination with the fact that Imatinib mesylate is mixed with a polymer coating on a stent. Such controlled release technique is, as acknowledged in the application (page 28, second paragraph), part of the common practice followed by persons skilled in the art. Additionally, the increase in stability of a therapeutic compound when it is mixed with a polymer can definitively not be considered as a surprising effect. It is an effect common to most drug to be stabilized and released over longer periods when admixed with a polymer for drug release.

The addition of a co-agent consists merely in a juxtaposition of features which effects is not more than an additive one.

The subject-matter of independent claims 9 and 10 can therefore not be considered as involving an inventive activity in the sense of Article 33(1) and (3) PCT.

8. No other claims could be identified which would contain a technical feature susceptible of being considered as involving an inventive contribution.

CLAIMS:

1. Use of N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine or a pharmaceutically acceptable salt or crystal form thereof, for the manufacture of a pharmaceutical for stabilizing vulnerable plaques in blood vessels of a subject in need of such a stabilization or for the prevention or reduction of vascular access dysfunction in association with the insertion or repair of an indwelling shunt, fistula or catheter in a subject in need thereof.

2. Use according to claim 1 for use in conjunction with one or more active co-agents.

3. Use according to claims 1 or 2 wherein 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide is in the form of the methanesulfonate salt.

4. Use according to one of claims 1 to 3 wherein 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide or a pharmaceutically acceptable salt or crystal form thereof is administered in a daily dose of 10 mg to 1000 mg.

5. Use according to any one of the preceding claims wherein 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]-benzamide or a pharmaceutically acceptable salt is administered about 7 days prior to access placement.

6. Use according to any one of the preceding claims wherein the vascular access dysfunction is selected from vascular access clotting, vascular access dysfunction associated with hemodialysis and vascular thrombosis.

7. Use according to any one of the preceding claims wherein the dosage is administered orally.

8. Use according to any one of the preceding claims wherein the subject is selected from a dialysis patient, e.g. hemodialysis patient, a cancer patient or a patient receiving total parenteral nutrition.

9. A drug delivery device or system comprising
i) a medical device adapted for local application or administration in hollow tubes
and
ii) a therapeutic dosage of N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine or a pharmaceutically acceptable salt or crystal form thereof being releasably affixed to the drug delivery device or system.

10. A drug delivery device or system comprising
i) a medical device adapted for local application or administration in hollow tubes
and
ii) a therapeutic dosage of N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine or a pharmaceutically acceptable salt or crystal form thereof,
and
iii) a therapeutic dosage of one or more active co-agents selected from a rapamycin derivative having mTOR inhibiting properties or rapamycin, an EDG-receptor agonist having lymphocyte depleting properties, a cox-2 inhibitor, pimecrolimus, a cytokine inhibitor, a chemokine inhibitor, an antiproliferative agent, a statin, a protein, growth factor or compound stimulating growth factor production that will enhance endothelial regrowth of the luminal endothelium, a matrix metalloproteinase inhibitor, a somatostatin analogue, an aldosterone synthetase inhibitor or aldosterone receptor blocker and a compound inhibiting the renin-angiotensin system,
each being releasably affixed to the drug delivery device or system.

11. A drug delivery device or system according to claim 10 wherein one or more active co-agents are selected from a calcineurin inhibitor, mycophenolic acid, 40-O-(2-hydroxyethyl)-rapamycin, rapamycin and midostaurin or a salt thereof or prodrug thereof.

12. Use of a drug delivery device or system according to any one of claims 9 to 11, for stabilizing vulnerable plaques in blood vessels, for the prevention or reduction of vascular access dysfunction in association with the insertion or repair of an indwelling shunt, fistula or catheter in a patient in need thereof.

13. Use of a drug delivery device or system according to anyone of claims 9 to 11 for preventing or treating smooth muscle cell proliferation and migration in hollow tubes or increased cell proliferation or decreased apoptosis or increased matrix deposition in a subject in need thereof.

14. A method for the prevention or reduction of vascular access dysfunction in association with the insertion or repair of an indwelling shunt, fistula or catheter, or actual treatment, in a subject in need thereof, which comprises administering a controlled delivery from a drug delivery medical device or system of a therapeutically effective amount of N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine or a pharmaceutically acceptable salt or crystal form thereof, optionally in conjunction with one or more active co-agents.

15. A method for preventing or treating smooth muscle cell proliferation and migration in hollow tubes, or increased cell proliferation or decreased apoptosis or increased matrix deposition in a subject in need thereof, comprising local administration of a therapeutically effective amount of N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine or a pharmaceutically acceptable salt or crystal form thereof, optionally in conjunction with a therapeutic dosage of one or more active co-agents selected from a rapamycin derivative having mTOR inhibiting properties or rapamycin, an EDG-receptor agonist having lymphocyte depleting properties, a cox-2 inhibitor, pimecrolimus, a cytokine inhibitor, a chemokine inhibitor, an antiproliferative agent, a statin, a protein, growth factor or compound stimulating growth factor production that will enhance endothelial regrowth of the luminal endothelium, a matrix metalloproteinase inhibitor, a somatostatin analogue, an aldosterone synthetase inhibitor or aldosterone receptor blocker and a compound inhibiting the renin-angiotensin system.